

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/56, 9/06	A1	(11) International Publication Number: WO 99/33471 (43) International Publication Date: 8 July 1999 (08.07.99)
(21) International Application Number: PCT/FI98/01000 (22) International Filing Date: 21 December 1998 (21.12.98) (30) Priority Data: 974610 23 December 1997 (23.12.97) FI (71) Applicant (for all designated States except US): LEIRAS OY [FI/FI]; P.O Box 415, FIN-20101 Turku (FI). (72) Inventors; and (75) Inventors/Applicants (for US only): KATILA, Kirsi [FI/FI]; Kallantie 115, FIN-23100 Mynämäki (FI). LEHTOLA, Veli-Matti [FI/FI]; Ilkanrinne 2 A 16, FIN-20810 Turku (FI). RANTALA, Pertti [FI/FI]; Kierrekuja 3, FIN-20660 Littoinen (FI). (74) Agent: TURUN PATENTTITOIMISTO OY; P.O. Box 99, FIN-20521 Turku (FI).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.
(54) Title: A GEL-FORM PHARMACEUTICAL PREPARATION (57) Abstract The invention relates to a pharmaceutical formulation which contains a corticosteroid and a solvent. According to the invention the formulation is brought to gel form by using a gellant which is a hydroxyalkyl cellulose, in particular hydroxyethyl cellulose or hydroxypropyl cellulose.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

A GEL-FORM PHARMACEUTICAL PREPARATION

The invention relates to a corticosteroid-containing pharmaceutical preparation intended for topical use.

Corticosteroids constitute a large group of compounds with a pregnene or pregnadiene backbone and with versatile
5 medical uses. In particular they are used topically as anti-inflammatory dermatological medicines. Examples of corticosteroids on the market include hydrocortisone, dexamethasone, betamethasone, methylprednisolone, prednisolone, prednisone, beclomethasone, fludrocortisone,
10 triamsinolone, desonide, fluprednidene, clobetasone, alclomethasone, momethasone, desoxymethasone, fluosinonide, budesonide and fluosinolone.

Common forms of preparations include solutions, ointments, creams and liniments. Certain ester-form glucocorticoids,
15 such as betamethasonide propionate, have also been prepared as a gel in which Carbomer, i.e. carboxyvinyl polymer, has been used as the gellant.

Hydrocortisone gels are not available on the market. Attempts to prepare a hydrocortisone gel by using
20 conventional gellants such as Carbomer polymer have failed owing to the poor stability of hydrocortisone.

We have now observed, surprisingly, that by using hydroxyalkyl cellulose, in particular hydroxyethyl cellulose, as the gellant, very stable corticosteroid gels
25 are obtained.

The characteristics of the invention are given in Claim 1.

A corticosteroid-containing pharmaceutical formulation according to the invention is characterized in that the

formulation has been brought to gel form by means of a gellant, the gellant being hydroxyalkyl cellulose.

The corticosteroid may be any pharmaceutically acceptable corticosteroid. Preferably the corticosteroid is
5 hydrocortisone.

According to a preferred embodiment, the hydroxyalkyl cellulose used as the gellant is hydroxyethyl cellulose or hydroxypropyl cellulose, in particular hydroxyethyl cellulose.

10 The solvent used is preferably a mixture of water and a lower alcohol, such as ethanol or propanol. A mixture of water and ethanol or of water and isopropanol is especially preferable.

Glycerol or propylene glycol is preferably added to the
15 formulation in order to prevent skin drying caused by the alcohol (ethanol). For this purpose it is also possible to add some oil component, such as Cetiol SN (cetearyl-isononanoate). It is also possible to add suitable perfumes and preservatives. Examples of suitable preservatives
20 include methylparahydroxybenzoate, propylparahydroxybenzoate and benzyl alcohol.

The invention is described in greater detail with the help of the following, non-limiting examples.

Example 1

25 Hydrocortisone gels in which hydroxyethyl cellulose (HEC) is used as the gellant

Four hydrocortisone-containing gel batches I, II, III and IV were prepared. Batches I and II were prepared on a laboratory scale (1000 g/batch) and batches III and IV were
30 prepared on an industrial scale (150 kg/batch). The soft

gels were packed into polyethylene tubes. The stability of the gels was monitored for 18 months (batch I), 12 months (batch II) and 3 months (batches III and IV). The gels were prepared as follows: HEC was added to a mixture of water and ethanol (containing only a portion of the ethanol) while stirring, and the mixture was allowed to gel. Thereafter the glycerol was added while stirring. The balance of the ethanol was added while stirring. Thereafter the active ingredient was added to the gel while stirring.

10 Gel compositions (mg/g):

	Batches I, III and IV	Batch II
Hydrocortisone	10.00	10.00
Hydroxyethyl cellulose	15.00	15.00
15 Glycerol (99.5 %)	60.00	-
Ethanol (96 %)	500.00	500.00
Purified water	415.00	475.00

Stability tests:

The batches were stored at a relative humidity of 60 %. The temperature was 25 °C (batches I, III and IV) and respectively 20 °C (batch II).

According to the objective, the amount of degradation products may be at maximum 5 %, the amount of hydrocortisone should be 9.0 - 11.0 mg/g, and the pH should be 5 - 8.5.

Results:**Batch I**

	Period of storage months	Degradation products %	Hydrocortisone mg/g	pH
5	Beginning of test	0.6	10.2	7.5
	3 months	0.7	10.1	5.8
	7 "	2.3	10.1	5.7
	12 "	1.9	10.1	5.7
	18 "	1.9	9.5	5.7

10 Batch II

	Period of storage months	Degradation products %	Hydrocortisone mg/g	pH
	Beginning of test	*)	*)	*)
	12 months	2.2	10.3	5.6

15 *) not determined

Batch III

	Period of storage months	Degradation products %	Hydrocortisone mg/g	pH
	Beginning of test	0.6	10.3	6.6
20	3 months	0.7	9.8	6.8

Batch IV

	Period of storage months	Degradation products %	Hydrocortisone mg/g	pH
	Beginning of test	0.55	10.2	7
25	3 months	0.8	10.2	7

The results show that all of the batches remained well within the guideline values as regards hydrocortisone concentration, hydrocortisone degradation products and pH.

Example 2

5 Hydrocortisone gels in which Carbomer or Stabileze polymer was used as the gellant

For the sake of comparison, four hydrocortisone gel formulations A, B, C and D were prepared, in which the gellant used was carboxyvinyl polymer Carbomer 980 or
10 Carbomer 940, or polymer Stabileze^R QM, which is a copolymer of methylvinyl ether and maleic acid anhydride, cross-bridged with 1,9-decadiene. These gellants yield a very low pH value (the pH of a 1 % aqueous dispersion of Carbomer polymer is 2.5 - 3.0), and therefore sodium hydroxide was
15 added to adjust the pH to the desired range. The auxiliary compositions and hydrocortisone concentrations of the preparations are shown in Table 1, which also shows the stabilities of the preparations.

Table 1 shows that, already after three months of storage,
20 a large quantity of degradation products of hydrocortisone had formed. After six months of storage the concentration of hydrocortisone degradation products in preparations A, B and D clearly exceeded the guideline values (guideline value at maximum 5 %), and the concentration of degradation
25 products in preparation C was also very high (4 %).

The examples given above clearly show that highly stable hydrocortisone gels are obtained by using hydroxyethyl cellulose as the gellant. Although test results have not been presented, it can be assumed that corresponding
30 results would be obtained also with respect to other corticosteroids and when using other hydroxyalkyl celluloses, in particular hydroxypropyl cellulose.

Table 1

Auxiliary composition		A	B	C	D
Carbomer 980 Carbomer 940 Stabileze QM Ethanol 96 % Sodium hydroxide Macrogol 400 Glycerol Propylene glycol Purified water Sodium medetate		1.0 %	1.0 %	-	-
		-	-	1.0 %	-
		-	-	-	1.0
		60.0 %	60.0 %	60.0 %	27.0 %
		0.06 %	0.06 %	0.015 %	0.135 %
		3.0 %	3.0 %	-	-
		10.0 %	8.0 %	10.0 %	-
		-	-	-	-
Initial value		24.94 %	26.84 %	27.98 %	27.0 %
		-	0.1 %	-	43.9 %
3 months	Hydrocortisone concentration	10.1 mg/g	10.2 mg/g	10.1 mg/g	10.7 mg/g
	Degradation products	none	1.7 %	1.1 %	1.4 %
	Hydrocortisone concentration	9.1 mg/g	9.7 mg/g	10.3 mg/g	9.8 mg/g
	Degradation products	6 %	6 %	2.9 %	4 %
6 months	Hydrocortisone concentration	9.2 mg/g	9.1 mg/g	9.5 mg/g	9.2 mg/g
	Degradation products	10 %	7 %	4 %	11 %

The above embodiments of the invention are only examples of the implementation of the idea of the invention. For a person skilled in the art it is clear that the various embodiments of the invention may vary within the claims
5 presented below.

CLAIMS

1. A pharmaceutical formulation comprising a corticosteroid and a solvent, characterized in that the formulation has been brought to gel form by using a gellant, the gellant being a hydroxyalkyl cellulose.
- 5 2. A formulation according to Claim 1, characterized in that the corticosteroid is hydrocortisone.
3. A formulation according to Claim 1 or 2, characterized in that the hydroxyalkyl cellulose is hydroxyethyl cellulose or hydroxypropyl cellulose.
- 10 4. A formulation according to Claim 1, 2 or 3, characterized in that the solvent is a mixture of water and a lower alcohol.
5. A formulation according to any of the above claims, characterized in that the corticosteroid is hydrocortisone,
15 the gellant is hydroxyethyl cellulose, and the solvent is a mixture of water and ethanol.
6. A formulation according to Claim 5, characterized in that it additionally contains glycerol.
7. A formulation according to Claim 5 or 6, characterized
20 in that it additionally contains propylene glycol.
8. A formulation according to Claim 5, characterized in that it contains approx. 0.1 % by weight hydrocortisone and 1 - 2 % by weight hydroxyethyl cellulose.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 98/01000

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/56, A61K 9/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3899580 A (JOSEPH L. O'NEILL ET AL), 12 August 1975 (12.08.75) --	1-8
X	WO 8809174 A1 (SCHERING CORPORATION), 2 December 1988 (02.12.88) --	1-8
X	US 5110809 A (JONAS WANG ET AL), 5 May 1992 (05.05.92) --	1-8
X	US 4267173 A (RICHARD W. DRAPER), 12 May 1981 (12.05.81), See especially Formulation 10 --	1-8

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

23 March 1999

Date of mailing of the international search report

27 -03- 1999

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. +46 8 666 02 86

Authorized officer

Göran Karlsson
Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 98/01000

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4604384 A (ROBERT A. SMITH ET AL), 5 August 1986 (05.08.86) --	1-8
X	US 4866050 A (DANIEL BEN-AMTZ), 12 Sept 1989 (12.09.89) -- -----	1-8

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/03/99

International application No.

PCT/FI 98/01000

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3899580 A	12/08/75	AU 5625573 A	05/12/74
		CA 1014856 A	02/08/77
		DE 2329130 A	20/12/73
		FR 2187340 A,B	18/01/74
		GB 1397893 A	18/06/75
		IE 37718 B	28/09/77
		NL 7307072 A	11/12/73
WO 8809174 A1	02/12/88	AU 616188 B	24/10/91
		AU 1941788 A	21/12/88
		CA 1307207 A	08/09/92
		DE 3872521 A	06/08/92
		DK 581989 A	20/11/89
		EP 0292893 A,B	30/11/88
		EP 0362270 A,B	11/04/90
		SE 0362270 T3	
		ES 2032898 T	01/03/93
		FI 95350 B,C	13/10/95
		FI 895482 D	00/00/00
		GR 3005762 T	07/06/93
		GR 3018818 T	30/04/96
		HK 60595 A	28/04/95
		IE 60546 B	27/07/94
		JP 2501739 T	14/06/90
		JP 2572124 B	16/01/97
		KR 9310584 B	30/10/93
		MX 9203285 A	01/07/92
		NO 175762 B,C	29/08/94
		US 4775529 A	04/10/88
US 5110809 A	05/05/92	AU 628632 B	17/09/92
		AU 6135090 A	27/02/92
		CA 1319105 A	15/06/93
		EP 0471872 A	26/02/92
		JP 4124134 A	24/04/92
		JP 5025856 B	14/04/93
		US 5002938 A	26/03/91
US 4267173 A	12/05/81	NONE	

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/03/99

International application No.

PCT/FI 98/01000

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4604384 A	05/08/86	AT 34918 T AU 558482 B DE 3376957 A EP 0112852 A,B SE 0112852 T3 WO 8400111 A	15/06/88 29/01/87 14/07/88 11/07/84 19/01/84
US 4866050 A	12/09/89	NONE	